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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/826,472

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EXAMINER

DUTT, ADITI

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/826,472	Applicant(s) MONJE ET AL.	
	Examiner Aditi Dutt	Art Unit 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 September 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-5,7,8,14,21 and 22 is/are pending in the application.
- 4a) Of the above claim(s) 7 and 8 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,3-5,14,21-22 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Status of Claims

1. The amendment filed on 9 September 2009 has been entered into the record and has been fully considered. Claims 1 and 22 are amended.
2. Claims 7 and 8 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim.
3. Claims 1, 3-5, 14 and 21-22, drawn to a method of reducing loss of neurogenesis resulting from neuroinflammation due to irradiation, are being considered for examination in the instant application.

Response to Amendment

Withdrawn objections and/or rejections

4. Upon consideration of the amendment to claims, rejection under 35 USC § 112, second paragraph is withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to

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a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. The rejection of claims 1, 3, 14, and 21-22, under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Brain Res 791: 352-356, 1998), in view of Plevova, (Radiol Oncol 36: 33-40, 2002), as evidenced by Kyrkanides et al. (Mol Brain Res. 104: 159-169, 2002), is applied to the amended claims, for reasons of record in the Office Action, dated 10 June 2009.
6. Applicant argues that Kondo does not teach that ischemia is correlated with neuroinflammation, or that neuroinflammation leads to loss of neurogenesis caused by cranial irradiation. Applicant further alleges that Plevova is a review article referring to the teachings of Tada et al on the effect of cranial irradiation on brain edema and necrosis, not on neuroinflammation and loss of neurogenesis. Applicant, therefore, concludes that the combination of references would "not predict any expectation of success" in contacting such individual with NSAID to produce the effect as claimed. Moreover, Applicant asserts that ischemia results in increased neurogenesis and submits articles (Liu et al. J Neurosci 18: 7768-7778, 1998; Yamashima et al. Biotech J 2: 596-607, 2007) to support the same. Applicant, therefore, alleges that Examiner has extrapolated beyond the teachings of the reference "indeed ignoring common knowledge in the art that ischemia stimulates neurogenesis". Furthermore, Applicants allege that the invention would not be obvious because of unexpected findings that neuroinflammation causes "a decrease in neurogenesis". Applicant argues that without the knowledge and establishment of a nexus between loss of

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neurogenesis and neuroinflammation, the claimed method is not obvious over the prior art. With respect to the Kyrkanides teachings, Applicant presents similar arguments stating that this reference also does not provide the connection between cranial irradiation induced neuroinflammation and loss of neurogenesis. Applicant provides a Declaration under 37 C.F.R. § 1.132 with regards to the Monje reference and emphasizes that this is the inventor's work, therefore, is not citable. Since Plevova and the other references do not cure the deficiencies of Kondo teachings, Applicant requests the withdrawal of the rejection.

7. Applicant's arguments are fully considered but not found to be persuasive. Firstly, both ischemia and cranial irradiation are known to cause neuroinflammation. For example, Price et al. (J Med Primatol 30: 81-87, 2001) teach that neuroinflammation is observed after irradiation of the brain in primates resulting in the activation of microglia/macrophages (abstract). Price et al. further provides histopathological changes of different regions of the brain (white matter and meninges) (page 83, Results, para 1; Table 2), resulting in gliosis and demyelination, that is one of the underlying causes for clinical symptoms like cognitive impairment (page 86, Discussion, para 1). Applicant's arguments with regards to ischemia and stimulation of neurogenesis are persuasive in part. It is noted that only certain regions of the brain demonstrate ischemia induced neurogenesis. For example, Liu et al (J Neurosci 18: 7768-7778, 1998 - submitted by Applicant) show that only the dentate gyrus elicits neurogenesis, whereas other regions of the CNS like hippocampal CA1 neurons, the entorhinal

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cortex and lateral striatum exhibit neuronal loss following global ischemia (Abstract; page 7771, col 2, para 4-5; Figures 5E, 6C). Similar findings were reiterated in the Yamashima reference (also submitted by Applicant) (abstract). The fact that some regions of the brain demonstrate neurogenesis after ischemia, Applicant's generalized allegation that ischemia results in neurogenesis is incorrect. Please note that the claims do not recite the effect on neurogenesis in any particular nuclei of the brain.

8. Applicant's assertion that neuroinflammation decreases neurogenesis is an unexpected finding of the inventors, a teaching not present in any of the cited references is not persuasive. First of all, a nexus between neuroinflammation and loss of neurogenesis is not derived from the instant claims as recited. On the contrary the limitation "wherein said loss of neurogenesis resulting from neuroinflammation due to said cranial irradiation in an individual is reduced" in claim 1, is recited as an intended outcome of the process, that essentially goes back to the preamble of the claim. It is reminded that "where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation" *Rowe v. Dror*, 112 F.3d 473, 478, 42 USPQ2d 1550, 1553 (Fed. Cir. 1997). No active method steps describing the observation of loss of neurogenesis is presented in the claim body. The person of ordinary skill would find it obvious to administer NSAID to an individual subjected to cranial irradiation, a state known to elicit neuroinflammation, whereby the inflammation is

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reduced, thus leading to a decrease in loss of neurogenesis. If applicant were to amend independent claim 1 to require an additional step, such as detecting the degree of neurogenesis after administration of the NSAID, as compared to an appropriate control, the claims may be allowable. Applicant is reminded not to introduce new matter in violation of 35 USC 112, first paragraph.

9. The Declaration by Dr. Theo Palmer is fully considered and has been found to be persuasive. Examiner is aware of the reference being published within one year of the filing date of the instant invention and therefore, was merely presented as an evidentiary support as a basis for depicting the state of the art at the time of filing of the instant application. However, based on Applicant's persuasive arguments, the reference is withdrawn from the rejection.
10. For reasons discussed above, it is reiterated that it would have been obvious to the person of ordinary skill in the art at the time the claimed invention was made to substitute the method of reducing neuroinflammation using NSAID or indomethacin due to cerebral ischemia as taught by Kondo et al. for a method comprising administering NSAID to an individual subjected to cranial irradiation induced neuroinflammation in view of Plevova and the evidentiary support of Kyrkanides et al. The combination of the above references proves that the knowledge and expertise for the claimed method for using anti-inflammatory NSAIDs in cranial irradiation induced neuroinflammation was known in the art and the therapeutic effects were expected to be successful. The prima facie

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obviousness of the claimed invention in view of the combined references, therefore, provides sufficient reasoning, and nullifies Applicant's allegations of the improper teachings in the individual references. Applicant's assertion of unexpected results does not overcome the rejection because of obvious expected properties taught in the prior art, either explicitly or implicitly. "Where the unexpected properties of a claimed invention are not shown to have a significance equal to or greater than the expected properties, the evidence of unexpected properties may not be sufficient to rebut the evidence of obviousness". *In re Nolan*, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977). Therefore, the instant invention as claimed in claims 1, 3, 14, and 21-22 as a whole was clearly prima facie obvious over the combined teachings of the prior art.

11. The rejection of claims 1, 3-5, 14, and 21-22 under 35 U.S.C. 103(a) as being unpatentable over Tada et al. (Neurosurgery 41: 209-219, 1997 – online publication 1-18 pages), in view of Plevova, (Radiol Oncol 36: 33-40, 2002), is applied to the amended claims, for reasons of record in the Office Action, dated 10 June 2009.
12. Applicant repeats the same arguments as stated above. Basically, Applicant asserts that Tada et al. do not teach cranial irradiation results in neuroinflammation, further resulting in loss of neurogenesis, and Plevova teachings do not cure the deficiencies of the primary reference.

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13. Applicant's arguments are fully considered, however, are not found to be persuasive for reasons detailed above. Therefore, the instant invention as claimed in claims 1, 3-5, 14, and 21-22 as a whole was clearly prima facie obvious over the combined teachings of the prior art.

14. The rejection of claims 1, 3-5, 14, and 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kondo et al. (Brain Res 791: 352-356, 1998), in view of Plevova, (Radiol Oncol 36: 33-40, 2002), is applied to the amended claims, for reasons of record in the Office Action, dated 10 June 2009.

15. Once again Applicant repeats the same arguments as stated above.

16. Applicant's arguments are fully considered, however, are not found to be persuasive for reasons detailed above for the same combination of references. Therefore, the instant invention as claimed in claims 1, 3-5, 14, and 21-22 as a whole was clearly prima facie obvious over the combined teachings of the prior art.

Conclusion

17. No claims are allowed.

18. **THIS ACTION IS MADE FINAL.**

19. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory

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action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Aditi Dutt whose telephone number is (571) 272-9037. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 5:00 p.m.
21. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.
22. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov/>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AD
29 December 2009

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
January 4, 2010